An Outline of the Common Transmissible Neoplastic Diseases of the Chicken

Production Research Report No. 129

Agricultural Research Service
UNITED STATES DEPARTMENT OF AGRICULTURE

An Outline of the Common Transmissible Neoplastic Diseases of the Chicken

By B. R. Burmester, *director*, and R. L. Witter, *research veterinarian*, Regional Poultry Research Laboratory
Animal Science Research Division, Agricultural Research Service

Comparative characteristics of the common transmissible neoplastic diseases of the chicken are outlined here to provide a readily available source of information for poultry diagnosticians and research workers who have some background training in avian pathology and also for students who are simultaneously making use of other sources for more comprehensive reading on this subject. For further study, we recommend chapter 15 (Neoplastic Diseases) in "Diseases of Poultry," (6th edition) edited by M. Hofstad, printed by the Iowa State University Press, Ames, Iowa.

The term "avian leukosis complex" has been omitted from the title of the present report. Research advances during the past few years have vastly increased our understanding of the etiology, pathogenesis, and epizootiology of avian neoplastic diseases. Although there is still much to be learned, these diseases do not present a "complex" as they did when that term was first adopted. Also, the neoplastic diseases can now be classified in terms of the causative viruses, thus allowing the use of more specific identifying terms.

Three etiologically distinct neoplastic diseases or disease groups are now recognized: (1) The leukosis/sarcoma group, (2) Marek's disease, and (3) reticuloendotheliosis.

The leukosis/sarcoma group includes lymphoid leukosis (LL), myeloblastosis, myelocytomatosis, erythroblastosis, and such solid tumors as fibrosarcomas, endotheliomas, hepatomas, nephroblastomas, and osteopetrosis. These tumors are caused by a number of closely related ribonucleic (RNA) viruses which have some properties in common with the myxovirus. By far the most commonly occurring neoplastic disease of this group is lymphoid leukosis.

Marek's disease, the second neoplastic disease, is extremely prevalent and is now known to be caused by a herpesvirus of the B group with many properties similar to those of cytomegaloviruses.

In these first two neoplastic diseases, tumors are a comparatively rare consequence of viral infection. Thus, most infected birds never develop manifestations of the disease. Because of this, evidence of infection alone is of little diagnostic value. A diagnosis of the cause of the symptoms, lesions, or death must instead be based on clinicopathologic evidence; for example, morphologic alterations, lesion distribution, and clinical signs. Consideration should also be given to age, morbidity, mortality, and other epizootiologic information.

The third neoplastic disease, reticuloendotheliosis, is caused by an RNA virus different from viruses of the leukosis/sarcoma group. Because clinical signs and lesions have not been reported to occur under natural conditions and because little is known concerning the distribution of infection, this disease will not be considered further in this report.

The comparative characteristics of the common transmissible neoplastic diseases of the chicken are given below.

This Production Research Report supersedes Production Research Report No. 94, "An Outline of the Diseases of the Avian Leukosis Complex"

Washington, D.C. Issued June 1971
For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402 - Price 25 cents

COMMON TRANSMISSIBLE NEOPLASTIC DISEASES

Item	THE LEUKOSIS/SARCOMA GROUP						MAREK'S DISEASE
	Lymphoid leukosis (LL)	Myeloblastosis (Leukemic)	Myelocytomatosis (Aleukemic or leukemic)	Erythroblastosis		Fibrosarcoma, endothelioma, hepatoma, and nephroblastoma	Osteopetrosis	
				Proliferative	Anemic			
Synonyms	Visceral lymphomatosis, lymphocytoma, big liver disease.	Granuloblastosis, myeloleukosis, diffuse myeloid leukosis.	Leukochloroma, myelocytoma, discrete myeloid leukosis, erythroleukosis.	Intravascular LL, erythroleukosis, erytbromyelosis.		None.	Marble bone, thick leg disease.	Neural lymphomatosis, fowl paralysis, range paralysis, neuritis, visceral lymphomatosis, acute leukosis, ocular lymphomatosis, gray eye, pearly eye, iritis, skin leukosis.
Definition	Autonomous proliferation of the respective immature blood elements with impairment of organ function.					Autonomous proliferation of fibroblasts, vascular endothelial, hepatic parenchymal, renal epithelial, and other cells.	Excessive proliferation of periosteal osteoblasts and deposition of hard bone.	Infiltration of lymphocytes and plasma cells, with progression to autonomous proliferation.
Early history	Caprini, 1896, first to describe; Ellermann and Bang, 1908, transmitted with filtrates and proved viral etiology of erythroblastosis; Burmester and others, 1946, showed viral etiology of LL and relation to erythroblastosis; Furth, 1933, transmitted myelocytomatosis with filtrates.					Rous, 1911, transmitted fibrosarcoma with virus; Furth, 1933, transmitted endothelioma; Carr, 1956, transmitted renal adenocarcinoma; Beard, 1968, transmitted hepatoma.	Pugh, 1927, described diffuse osteopetrosis; Jungherr, 1935, transmitted and indicated relation to lymphomatosis.	Marek, 1907, and Kaupp, 1921, described the disease, and the latter associated blindness with paralysis. Van der Walls and Winkler-Junius, 1924, and Pappenheimer and others, 1926, described and transmitted the disease. The virus was isolated and identified by Churchill and coworkers in England and by Solomon, Nazerian, and coworkers in America, 1967.
Etiology:								
Morphology	A family of closely related, ether-sensitive, enveloped, RNA viruses; ovoid or spherical and about 80 mμ in diameter with an electron dense core.							DNA, ether-sensitive, herpesvirus with 162 capsomeres and icosahedral symmetry; capsid 85–100 mμ in diameter; enveloped virion greater than 150 mμ.
Viability	Killed by common disinfectants. Remains viable for long periods at −76° C., but rapidly inactivated at higher temperatures. Half life at 37° is 260 minutes, at 50° it is 10 minutes, and at 60° it is 1 minute.							Mature enveloped virus from feathers, dander, and litter survives at least 16 weeks at room temperature but is destroyed by heat and disinfectants. Virus in blood and most other tissues is cell associated and infectivity depends upon cell viability.
Tissue culture	Viruses grow in many different cell cultures of genetically susceptible avian embryos. Morphological alterations are caused in chick embryo fibroblast cultures by sarcoma, endothelioma and myelocytoma viruses in short periods and by LL virus in long periods. Myeloblastosis virus alters yolk sac cultures.							Virus grows in chick kidney cell and duck embryo fibroblast cultures, producing discrete cytopathic areas with syncytia and DNA-containing intranuclear inclusion bodies.
Detection methods	All viruses of this group can be detected by: (1) COFAL test, (2) RIF test, (3) NP cell activation test, and (4) FA staining test. Only Rous sarcoma, myelocytomatosis, and myeloblastosis viruses alter cell culture and only the Rous sarcoma virus alters embryonated eggs. Antibody to any virus of this group can be assayed by the neutralization test, using Rous sarcoma virus. The neutralization, RIF, and FA tests are subgroup specific; hence, reagents representing each subgroup to be tested must be used. Examination of blood and tumor smears and section of bursa of Fabricius are useful aids in detecting specific infection of chickens.							Virus can be detected by inoculation of cell culture, embryo (yolk sac), or chicks and observation for virus plaques, pocks on the CAM or lesions, respectively. Chick infection can be established by: (1) Virus isolation, (2) demonstration of antibody, (3) detection of typical lesions, or (4) detection of antigens by the direct FA test in feather follicle epithelium, bursa, or other tissues.
Immunology	Four distinct virus subgroups, A, B, C, and D, have been identified on the basis of virus neutralization, interference, and host range. Complement fixing antigen is common to all subgroups. Antigenic variation is unrelated to variation in oncogenic spectrum. Antibody does not protect against tumor but maternal antibody gives partial protection. Most chickens have subgroup A antibody and a few have subgroup B.							Antibody is detected by agar gel precipitin test, indirect FA test, and neutralization of a related turkey herpesvirus. Inoculation with avirulent strains protects against disease but not infection. Parental antibody protects to some extent against early exposure. So-called "A" and "BC" antigens have been identified, but some virus strains lack "A" antigen.

COMMON TRANSMISSIBLE NEOPLASTIC DISEASES—Continued

Item	THE LEUKOSIS/SARCOMA GROUP							MAREK'S DISEASE
	Lymphoid leukosis (LL)	Myeloblastosis (Leukemic)	Myelocytomatosis (Aleukemic or leukemic)	Erythroblastosis		Fibrosarcoma, endothelioma, hepatoma, and nephroblastoma	Osteopetrosis	
				Proliferative	Anemic			
Epizootiology: Distribution	Found wherever poultry are kept.							Found wherever poultry are kept.
Occurrence	Commonly enzootic, especially in commercial flocks, rarely epizootic.	Rare.	Sporadic.	Sporadic.		Rare.	Rare to sporadic.	Commonly enzootic, often assumes epizootic proportions.
Mortality	Low to moderate rate over long period.	Very low rate.	Very low rate.	Usually very low rate, rarely high.		Very low rate.	Very low rate.	Variable, dependent on virulence of virus and other factors; often moderate to high rate over a short period, followed by low rate over a long period.
Transmission (Natural).	Carriers—common at all ages and for long periods; congenital (egg)—much; direct contact—moderate; contaminated environment—little; airborne—little, if any.	Primarily unknown; some direct contact transmission occurs.						Carriers—common at all ages and for long periods; very contagious; airborne route—most important; feathers, dander, dust, and litter—infectious; congenital (egg) transmission—absent or of no significance.
Susceptible hosts	Chickens most susceptible; similar lesions observed in turkeys and quail.	Chickens most susceptible; variable experimental transmission to guinea fowl, turkeys, doves, and pheasants; certain strains of Rous sarcoma will cause tumors in some mammals.						Chickens most susceptible; similar lesions observed in ducks, pheasants, turkeys, quail, and other birds; MD virus isolated from chickens and quail; a related but nonpathogenic herpesvirus isolated from turkeys.
Factors influencing susceptibility: Genetic	Separate alleles determine resistance to virus infection with each of 4 identified subgroup viruses. Other genetic factors determine resistance to tumor induction or regression of tumors.							Variation in resistance to virus infection not yet described. Resistance to tumor induction markedly influenced by one or more genetic factors.
Age	Susceptibility decreases with age.							Decreased susceptibility with age observed in some trials.
Seasonal	No effect.							Unknown, condemnation of broilers for MD higher in winter months.
Sex	Female more susceptible.	Susceptibility not affected by sex of chickens.					Males more susceptible.	Females more susceptible.
Maternal antibody.	High levels decrease probability of disease resulting from early exposure.							High levels decrease probability of disease resulting from early exposure.
Symtomatology: Incubation period	16 to 32 weeks, can be as long as 18 months.	3 to 16 weeks.	4 to 10 weeks.	3 to 16 weeks.		Usually 3 to 20 weeks but can be years.		2 to 20 weeks, can be as long as 18 months.
Signs	Enlarged abdomen, palpable liver and bursa of Fabricius, weakness.	Paleness, weakness, emaciation, sometimes palpable liver.	Nodules on cranium and other bones, latter easily broken, weakness, emaciation.	Weakness, cyanosis, emaciation.	Weakness, paleness, emaciation, ascites.	Palpable tumors in muscle and skin, enlarged abdomen, weakness.	Stilted gait, enlargement of shaft of long bones, paleness, weakness.	Incoordination; paresis of leg, wing, neck; emaciation; dehydration; dyspnea; weakness; enlargement of feather follicles; leathery skin; palpable skin tumors; abnormal, grayish, constricted, irregular, or immobile iris.

COMMON TRANSMISSIBLE NEOPLASTIC DISEASES—Continued

Item	THE LEUKOSIS/SARCOMA GROUP							MAREK'S DISEASE
	Lymphoid leukosis (LL)	Myeloblastosis (Leukemie)	Myelocytomatosis (Aleukemie or leukemie)	Erythroblastosis		Fibrosarcoma, endothelioma, hepatoma, and nephroblastoma	Osteopetrosis	
				Proliferative	Anemic			
Pathology:								
Pathogenesis	All virus strains or isolates are multipotent, causing several types of tumors in susceptible chickens. Large doses of virus are needed to cause myeloblastosis, erythroblastosis, and sarcoma. When exposure is very early and heavy, a permanent virema with immunological tolerance occurs and antibodies are not produced. When exposure is late or light, viremia disappears and antibodies are produced.							Exposure to virulent strains results in development of microscopic lesions and virus excretion in 1 to 2 weeks. Antibody is detected 2 to 4 weeks after exposure. Virus and antibodies persist for long periods. Lesions persist or increase in size for various periods but usually regress and disappear. Continued progression of lesion development may cause death. Lesions are usually lymphoproliferative (ranging from frank neoplasia to infiltration of inflammatory type cells), but degenerative lesions may also be observed. The latter occur mostly in the feather follicle, bursa of Fabricius, and thymus. Mature, enveloped herpesvirus produced in feather follicle presumably is the natural source of airborne and environmental contagion.
	Whether viremia is persistent or transient, chickens may appear normal and histopathologic lesions may be absent for long periods. Lymphoid cells of bursa of Fabricius are transformed at 8 to 12 weeks after exposure, and tumor cells later metastasize to visceral organs, causing tumors. Shedding of virus into the egg, the nasal and salivary secretions, and droppings occurs consistently in viremic chickens and sporadically in chickens having antibodies.	After onset of viremia, there is a proliferation of the primitive blood elements, first in the bone marrow and then in parenchymatous organs and some tissues. If the course is not rapid, antibodies are formed.				After onset of viremia, there is a proliferation of respective tissue elements.		
Cell types	Predominantly lymphoblasts, with variable numbers of small to large lymphocytes.	Myeloblast.	Myelocyte with wide range in differentiation, with and without granules.	Erythroblast, polychrome erythrocytes.	Polychrome erythrocytes, few blast cells.	Fibroblast, endothelial cell, epithelial cell.	Osteoblasts.	Small, medium, and large lymphocytes; plasma cells, dark staining Marek's cells, reticular cells; in some cases, many lymphoblasts.
Morphology (gross):								
Liver	Usually tumorous, diffuse or focal and enlarged 2 to 10 times, tumor grayish white.	Usually tumorous, diffuse and moderately enlarged, tumor grayish white.	Often tumorous, usually nodular white masses, slight or no enlargement.	Usually involved, cherry to mahogany red.	Pale, often smaller than normal.	Fibrosarcomas rare; red or white endothelial tumors. Hepatoma—focal, diffuse, moderately enlarged, pale red.	No changes or may be fibrotic.	Seldom to often tumorous, diffuse or focal and enlarged 2 to 5 times.
Spleen	Usually tumorous, diffuse or focal and enlarged 2 to 20 times.	Usually tumorous, diffuse and enlarged 2 to 20 times.	Often tumorous, nodular white masses, slight or no enlargement.	Cherry red or darkened, enlarged 2 to 10 times	Pale, enlarged ½ to 2 times.	Occasional fibrosarcoma or endothelial tumors.	Atrophy, sometimes with pigmentation.	Seldom to often tumorous, diffuse or focal and enlarged 2 to 20 times.
Pancreas	Seldom tumorous, firm, whitish nodular tumors.	Rarely tumorous.	Rarely tumorous, white nodular tumors.	Usually no changes, occasional petechia.		Occasional fibrosarcoma or endothelial tumors.	No changes.	Occasionally diffuse and enlarged.

COMMON TRANSMISSIBLE NEOPLASTIC DISEASES—Continued

Item	THE LEUKOSIS/SARCOMA GROUP							MAREK'S DISEASE
	Lymphoid leukosis (LL)	Myeloblastosis (Leukemie)	Myelocytomatosis (Aleukemie or leukemie)	Erythroblastosis		Fibrosarcoma, endothelioma, hepatoma, and nephroblastoma	Osteopetrosis	
				Proliferative	Anemic			
Morphology (gross)—Con.								
Lungs	Rarely tumorous, usually focal, firm, and gray, occasionally diffuse.	Occasional tumor similar to LL.	Occasional white nodular tumors.	No changes or congestion.	Pale, often edematous.	Occasional fibrosarcoma endothelial tumors.	No changes.	Commonly tumorous, diffuse or nodular, firm, yellow gray.
Muscle	Very rarely tumorous, diffuse or nodular.	No changes.	Rare white tumors.	No changes.	Pale.	Common site of fibrosarcomas, firm, fibrous, sometimes with mucinous fluid, endotheliomas may occur.	Muscle atrophy of affected appendages.	Seldom to frequently tumorous, nodular or streaking between muscle bundles, gray to yellowish white, with or without gelatinous fluid, occasional massive diffuse tumors, atrophy of muscles that are innervated by affected nerves.
Skin	Very rare focal tumors.	No changes.	No changes.	No changes.	No changes.	Occasional fibrosarcoma or endothelial tumors, occasional ulceration.	No changes.	Seldom to frequently tumorous, nodular enlargement of feather follicles, dark yellow to gray, occasional general thickening and ulceration, changes best observed after removal of feathers.
Bone	No changes.	No changes.	Usually tumorous; white to yellow nodules on periosteum of ribs, skull, sternum, pelvis, and other bones; affected bones may be easily fractured.	No changes.		No changes.	Always involved, rough surface and thickening periosteum, moderate to marked enlargement of diaphysis of long bones; very hard and they fracture with difficulty.	No changes.
Peripheral and autonomic nerves and ganglia.	Very rare extension of tumor to nerves.	No changes.	No changes.	No changes.		Rare fibrosarcoma.	No changes.	Usually involved, enlarged, translucent gray or yellow, loss of striations in one or more nerves and ganglia, grossly normal nerves may have extensive microscopic cellular infiltration.
Brain and spinal cord.	Rare involvement of meninges with extension into brain.	No changes.	No changes.	No changes.		No changes.	No changes.	Usually no gross changes, but often microscopic perivascular infiltrations.
Eye	No changes.	No changes.	No changes.	No changes.		No changes.	No changes.	Rarely involved, uneven depigmentation of iris with irregularity of border and constriction of pupil.
Histopathology	Mostly lymphoblasts; often very anaplastic; some small to large lymphocytes in focal or coalescing extravascular accumulations; in early stages, cells of follicles of bursa of Fabricius transform to lymphoblasts and may grow to massive tumors and metastasize; bursal tumors are always intrafollicular.	Massive extravascular accumulations of myeloblasts and immature myelocytes in bone marrow, liver, kidney, and spleen; focal proliferations in extra sinusoidal spaces—in bone marrow first and then in parenchymatous organs.	Proliferation and accumulation of granulocytes and myelocytes in marrow; compact masses of myelocytes having acidophilic granulation associated with bone, liver, and other viscera.	Accumulation of erythroblasts in sinusoids of bone marrow, spleen, and liver, with presence of blastic cells in vessels.	Bone marrow aplastic or increase in polychrome erythrocytes.	Sarcoma—compact masses of fusiform fibroblasts giving tumor an irregular, whirled appearance. Endothelioma—proliferations of vascular endothelium into compact or cavernous masses; the latter are hemangioendotheliomas. Nephroblastoma—proliferation of endothelial and connective tissue elements of the kidney; tumors may be solid or cystic.	Hyperplasia of periosteum; deposition of fibrous, cellular, spongy bone on the surface of the cortical bone; spongy bone becomes calcified, leaving irregular spaces.	Nerve—3 types described: (1) Proliferation of lymphocytes, degenerating MD cells, some demyelination, and Schwann cell proliferation; (2) enlargement of nerve with edematous fluid between fibers, accompanied by scattered infiltration with lymphocytes and plasma cells and degeneration of neurites; (3) mild lesions with plasma cells, considered a regressive process. Bursa of Fabricius—interfollicular infiltration of pleomorphic lymphocytes, sometimes with necrobiosis. Other tissue—usually a perivascular accumulation of lymphoid and plasma cells; may progress to tumor; degenerative, necrobiotic changes in feather follicle epithelium (intranuclear and intracytoplasmic inclusions present), bursa of Fabricius, thymus, bone marrow; most common when antibody-free chicks are given massive virus exposure.

COMMON TRANSMISSIBLE NEOPLASTIC DISEASES—Continued

Item	THE LEUKOSIS/SARCOMA GROUP							MAREK'S DISEASE
	Lymphoid leukosis (LL)	Myeloblastosis (Leukemic)	Myelocytomatosis (Aleukemic or leukemic)	Erythroblastosis		Fibrosarcoma, endothelioma, hepatoma, and nephroblastoma	Osteopetrosis	
				Proliferative	Anemic			
Diagnosis: Etiology	Laboratory tests for detection of virus and antibody are available; however, mixed infections are common and such tests are of little or no value in distinguishing lesions of LL from those of MD.							
Epizootiology	Sporadic occurrence 4 months after exposure, low to moderate rate of mortality, and almost complete absence of paretic signs.							Occurs as early as 2 weeks of age but usually after 6 weeks; peak of mortality at 12 to 30 weeks, often with paralysis.
Gross pathology	Small to large lymphoid tumors of plica of bursa of Fabricius; diffuse or focal tumor of liver, spleen, and other viscera.	Pale, enlarged liver and spleen; grayish-white bone marrow.	Nodular tumors of cranium and ribs.	Liver and bone marrow congested, cherry red.	Anemia; pale to yellow bone marrow.	Characteristic tumors.	Thickened bone, especially the diaphysis, rough and hard.	Enlarged nerves; irregular and discolored iris; enlarged feather follicles; tumors of gonad, heart, lung, muscle; bursa often atrophied, rare diffuse tumor of wall.
Histopathology	Focal or coalescing accumulations of lymphoblasts with pyroninophilic cytoplasms, bursa with intrafollicular tumor.	Extravascular accumulations of myeloblasts, especially in bone marrow, liver, and spleen.	Massive accumulations of myelocytes, usually with eosinophilic granules.	Intravascular accumulations of erythroblasts in bone marrow, liver, spleen.	Aplastic bone marrow, polychrome erythrocytes.	Characteristic histopathologic features.	Hypertrophy of periosteum, excessive and abnormal bone, atrophied bone marrow.	Pleomorphic population of lymphocytes, some plasma cells and occasional MD cells, only a few pyroninophilic cells, bursa rarely involved with interfollicular tumor.
Differential diagnosis.[1]	Visceral lesions of MD, pullorum disease, tuberculosis, enterohepatitis, Hjarre's disease, fatty degeneration of liver, myeloblastosis, erythroblastosis.	LL and conditions listed under LL, erythroblastosis, myelocytomatosis.	Tuberculosis, myeloblastosis, LL, pullorum disease.	Passive congestion due to a variety of infectious agents, myelocytomatosis, myeloblastosis.	Anemia due to malnutrition, toxic agents, hemorrhagic disease.	Muscle necrosis, granuloma, hemorrhage, ovarian tumor, LL.	Callus after fracture, perosis, thickening due to age, osteomyelosclerosis.	Viscera—LL, transient lymphoid reaction in gonad and heart due to various antigenic stimuli (especially LL virus), conditions listed under LL, carcinoma of ovary, fibrosarcoma, infectious bursal disease. Nerve—reticuloendotheliosis virus infection, riboflavin deficiency. Skin—dermatitis, xanthomatosis. Oculi—genetic gray eye, cataracts, bacterial infections.
Prognosis (individual and flock).	Unfavorable. Rarely apparent recovery or loss of signs. Mortality within the infected flocks usually continues at low to moderate rates for several weeks or months. No known procedure will reverse natural course of disease.							Poor in birds with gross lesions or clinical signs. Some birds apparently recover. No known procedure will reverse natural course of disease.
Prophylaxis	Recommended procedures include: (1) Obtaining progeny of genetically resistant chickens; (2) obtaining progeny from infection-free breeding stock; (3) strict sanitation and "all in, all out" management.							Recommended procedures include: (1) Obtaining progeny of genetically resistant chickens; (2) isolation rearing, coupled with strict sanitation and "all in, all out" management; (3) controlled exposure of chicks to used litter, preferably from old hens with low MD losses. However, none of these procedures is fully effective. Potentially better procedures include: (1) Vaccinating chicks with avirulent herpes virus strains from chickens or turkeys and (2) isolation rearing in housing supplied with biologically filtered air under positive pressure.

[1] For more information, see U.S. Department of Agriculture Technical Bulletin 1412, "The Differential Diagnosis of Lymphoid Leukosis and Marek's Disease."

U. S. GOVERNMENT PRINTING OFFICE : 1971 O - 415-361